Amendments to the Claims:

This listing of claims replaces all prior versions and listings of claims in the application:

Listing of Claims:

1. (Canceled)

2. (Currently amended) The method of claim ~~1~~ 41, wherein the TAK1 and/or the TAB1 is fused with a peptide.

3. (Currently amended) The method of claim ~~1~~ 41, wherein the TAK1 or the TAB1 is linked to a support.

4. (Currently amended) The method of claim ~~1~~ 41, wherein a label is attached to the TAK1 or the TAB1 and ~~wherein~~ the binding is detected by detecting or measuring the label.

5. (Currently amended) The method of claim ~~1~~ 41, wherein the binding is detected by detecting or measuring the TAB1 bound to the TAK1 with a primary antibody against TAB1 or a primary antibody against ~~the~~ a peptide fused with the TAB1.

6. (Currently amended) The method of claim ~~1~~ 41, wherein the binding is detected by detecting or measuring the TAK1 bound to the TAB1 with a primary antibody against TAK1 or a primary antibody against ~~the~~ a peptide fused with the TAK1.

7. (Currently amended) The method of claim ~~1~~ 41, wherein the binding is detected by detecting or measuring the TAB1 bound to the TAK1 with a primary antibody against the TAB1 or a primary antibody against ~~the~~ a peptide fused with TAB1, and a secondary antibody against the primary antibody.

8. (Currently amended) The method of claim ~~1~~ 41, wherein the binding is detected by detecting or measuring the TAK1 bound to the TAB1 with a primary antibody against TAK1 or a primary antibody against ~~the~~ a peptide fused with the TAK1, and a secondary antibody against the primary antibody.

9. (Currently amended) The method of claim ~~5~~ 7, wherein the primary antibody or the secondary antibody is labeled with a radioisotope, enzyme, or fluorescent substance.

10. (Currently amended) The method of claim 2, wherein the binding is detected ~~with, as an index,~~ as a change in the expression level of a reporter gene which is activated in response to the binding.

11. (Currently amended) The method of claim 10, wherein the reporter gene ~~is~~ encodes luciferase, chloramphenicol acetyltransferase, green fluorescent protein, or β-galactosidase.

12. (Withdrawn) A method for screening compounds inhibiting signal transduction through inflammatory cytokines, the method comprising the steps of:

(a) contacting a test sample with TAK1;

(b) detecting phosphorylation by the TAK1; and

(c) selecting a compound inhibiting the phosphorylation.

13. (Withdrawn) A method for screening compounds inhibiting signal transduction through inflammatory cytokines, the method comprising the steps of:

(a) contacting a test sample with TAK1 and TAB1;

(b) detecting phosphorylation by the TAK1; and

(c) selecting a compound inhibiting the phosphorylation.

14. (Withdrawn) The method of (12) or (13), wherein a substrate for the TAK1 is added and wherein the phosphorylation of the substrate by the TAK1 is detected.

15. (Withdrawn) The method of (14), wherein the substrate for the TAK1 is MKK6 and/or MKK3.

16. (Withdrawn) The method of any one of (12) to (15), wherein the TAK1 is fused with a peptide.

17. (Withdrawn) The method of any one of (12) to (16), wherein the TAK1 is linked to a support.

18. (Withdrawn) A method for screening compounds inhibiting signal transduction through inflammatory cytokines, the method comprising the steps of:

(a) introducing a test sample into and/or contacting the sample with cells expressing TAK1;

(b) detecting and/or measuring a biological activity transduced through the TAK1; and

(c) selecting a compound reducing the biological activity.

19. (Withdrawn) The method of (18), wherein the biological activity is a biological activity of inflammatory cytokines.

20. (Withdrawn) The method of (18), wherein the biological activity is detected with, as an index, change in the expression level of a reporter gene which is activated in response to the activity.

21. (Withdrawn) A method for screening compounds inhibiting signal transduction through inflammatory cytokines, the method comprising the steps of:

(a) introducing a test sample into and/or contacting the sample with cells expressing TAK1 and TAB1;

(b) detecting and/or measuring a biological activity transduced through the TAK1 and the TAB1; and

(c) selecting a compound reducing the biological activity.

22. (Withdrawn) The method of (21), wherein the biological activity is a biological activity of IL-1 or TNF.

23. (Withdrawn) The method of (21), wherein the biological activity is detected with, as an index, change in the expression level of a reporter gene which is activated in response to the activity.

24. (Withdrawn) The method of (20) or (23), wherein the reporter gene is luciferase, chloramphenicol acetyltransferase, green fluorescent protein, or β-galactosidase.

25. (Withdrawn) The method of any one of (18) to (24), wherein an inflammatory stimulus is given to cells and wherein the biological activity transduced through TAK1 or through TAK1 and TAB1 is detected and/or measured.

26. (Withdrawn) The method of (25), wherein the inflammatory stimulus is IL-1, TNF, or LPS.

27. (Currently amended) The method of claim ~~1~~ 41, wherein the inflammatory cytokine is IL-1, TNF, IL-10, or IL-6.

28. (Withdrawn) A compound for inhibiting signal transduction through inflammatory cytokines, the compound that can be isolated by the method of any one of (1) to (27).

29. (Withdrawn) A pharmaceutical composition comprising as an active ingredient the compound of (28).

30. (Withdrawn) An inhibitor of the signal transduction through inflammatory cytokines, the inhibitor having an activity of inhibiting signal transduction through TAK1.

31. (Withdrawn) An inhibitor of the activity of inflammatory cytokines, the inhibitor having an activity of inhibiting signal transduction through TAK1.

32. (Withdrawn) An inhibitor of the production of inflammatory cytokines, the inhibitor having an activity of inhibiting signal transduction through TAK1.

33. (Withdrawn) A pharmaceutical composition for inhibiting signal transduction through inflammatory cytokines, the pharmaceutical composition comprising as an active ingredient a compound inhibiting signal transduction through TAK1.

34. (Withdrawn) A pharmaceutical composition for inhibiting the activity of inflammatory cytokines, the pharmaceutical composition comprising as an active ingredient a compound inhibiting signal transduction through TAK1.

35. (Withdrawn) A pharmaceutical composition for inhibiting the production of inflammatory cytokines, the pharmaceutical composition comprising as an active ingredient a compound inhibiting signal transduction through TAK1.

36. (Withdrawn) The pharmaceutical composition of any one of (33) to (35), wherein the pharmaceutical composition is an anti-inflammatory agent.

37. (Withdrawn) The pharmaceutical composition of any one of (33) to (36), wherein the compound is a compound inhibiting binding between TAK1 and TAB1.

38. (Withdrawn) The pharmaceutical composition of any one of (33) to (36), wherein the compound is a compound inhibiting phosphorylation by TAK1.

39. (Withdrawn) The pharmaceutical composition of any one of (33) to (38), wherein the compound is a compound that can be isolated by the method of any one of (1) to (27).

40. (Withdrawn) The pharmaceutical composition of any one of (33) to (39), wherein the inflammatory cytokine is IL-1, TNF, IL-10, or IL-6.

41. (New) A screening method comprising:

(a) providing a sample comprising a TAK1 and a TAB1;

(b) contacting the sample with a compound;

(c) detecting binding between the TAK1 and the TAB1;

(d) selecting the compound if binding between the TAK1 and TAB1 is inhibited in the sample compared to a control; and

(e) testing the selected compound to determine whether it inhibits expression of an inflammatory cytokine in a cell or cell-free system that comprises a TAK1, a TAB1, and a gene encoding the inflammatory cytokine,

wherein the TAK1 of (a) is selected from the group consisting of

(i) a protein comprising amino acids 76 to 303 of SEQ ID NO:2;

(ii) a protein that binds to the TAB1 of (a) and comprises amino acids 76-303 of SEQ ID NO:2, with one to twenty amino acids substituted, deleted, and/or added; and

(iii) a protein that binds to the TAB1 of (a) and comprises an amino acid sequence encoded by a DNA sequence that hybridizes with the complement of nucleotides 408 to 1091 of SEQ ID NO:1 under washing conditions of 42°C, 5 x SSC, 0.1% sodium dodecyl sulfate, and 50% formamide; and

wherein the TAB1 of (a) is selected from the group consisting of

(iv) a protein comprising amino acids 437 to 504 of SEQ ID NO:4;

(v) a protein that binds to the TAK1 of (a) and comprises amino acids 437-504 of SEQ ID NO:4, with one to twenty amino acids substituted, deleted, and/or added; and

(vi) a protein that binds to the TAK1 of (a) and comprises an amino acid sequence encoded by a DNA that hybridizes with the complement of nucleotides 1338 to 1541 of SEQ ID NO:3 under washing conditions of 42°C, 5 x SSC, 0.1% sodium dodecyl sulfate, and 50% formamide.

42. (New) The method of claim 41, wherein the TAK1 of (a) comprises amino acids 76 to 303 of SEQ ID NO:2.

43. (New) The method of claim 41, wherein the TAK1 of (a) is a protein that binds to the TAB1 of (a) and comprises amino acids 76-303 of SEQ ID NO:2, with one to twenty substitutions, deletions, and/or additions.

44. (New) The method of claim 41, wherein the TAK1 of (a) is a protein that binds to the TAB1 of (a) and comprises amino acids 76-303 of SEQ ID NO:2, with one to ten substitutions, deletions, and/or additions.

45. (New) The method of claim 41, wherein the TAK1 of (a) is a protein that binds to the TAB1 of (a) and comprises amino acids 76-303 of SEQ ID NO:2, with one or two substitutions, deletions, and/or additions.

46. (New) The method of claim 41, wherein the TAK1 of (a) is a protein that binds to the TAB1 of (a) and comprises an amino acid sequence encoded by a DNA that hybridizes with the complement of nucleotides 408 to 1091 of SEQ ID NO:1 under washing conditions of 42°C, 5 x SSC, 0.1% sodium dodecyl sulfate, and 50% formamide.

47. (New) The method of claim 41, wherein the TAK1 of (a) is a protein that binds to the TAB1 of (a) and comprises an amino acid sequence that is encoded by a DNA that hybridizes

with the complement of nucleotides 408 to 1091 of SEQ ID NO:1 under washing conditions of 60°C, 0.1 x SSC, and 0.1% sodium dodecyl sulfate.

48. (New) The method of claim 41, wherein the TAB1 of (a) comprises the amino acids 437 to 504 of SEQ ID NO:4.

49. (New) The method of claim 41, wherein the TAB1 of (a) is a protein that binds to the TAK1 of (a) and comprises amino acids 437-504 of SEQ ID NO:4, with one to twenty amino acids substituted, deleted, and/or added.

50. (New) The method of claim 41, wherein the TAB1 of (a) is a protein that binds to the TAK1 of (a) and comprises amino acids 437-504 of SEQ ID NO:4, with one to ten amino acids substituted, deleted, and/or added.

51. (New) The method of claim 41, wherein the TAB1 of (a) is a protein that binds to the TAK1 of (a) and comprises amino acids 437-504 of SEQ ID NO:4, with one or two amino acids substituted, deleted, and/or added.

52. (New) The method of claim 41, wherein the TAB1 of (a) is a protein that binds to the TAK1 of (a) and comprises an amino acid sequence encoded by a DNA that hybridizes with the complement of nucleotides 1338 to 1541 of SEQ ID NO:3 under washing conditions of 42°C, 5 x SSC, 0.1% sodium dodecyl sulfate, and 50% formamide.

53. (New) The method of claim 41, wherein the TAB1 of (a) is a protein that binds to the TAK1 of (a) and comprises an amino acid sequence encoded by a DNA that hybridizes with the complement of nucleotides 1338 to 1541 of SEQ ID NO:3 under washing conditions of 60°C, 0.1 x SSC, and 0.1% sodium dodecyl sulfate.

54. (New) The method of claim 41, wherein the inflammatory cytokine is IL-1.

55. (New) The method of claim 41, wherein the inflammatory cytokine is TNF.

56. (New) The method of claim 41, wherein the inflammatory cytokine is IL-6.

57. (New) The method of claim 41, wherein the inflammatory cytokine is IL-10.

58. (New) The method of claim 41, wherein step (e) comprises contacting the cell or cell-free system with a substance that induces inflammation.

59. (New) The method of claim 58, wherein the substance is a lipopolysaccharide or an inflammatory cytokine.

60. (New) The method of claim 58, wherein the substance is IL-1 or TNF.

61. (New) A screening method comprising

(a) identifying a compound as an inhibitor of inflammatory cytokine activity;

(b) providing a sample comprising a TAK1 and a TAB1;

(c) contacting the sample with the compound;

(d) detecting binding between the TAK1 and the TAB1; and

(e) selecting the compound if binding between the TAK1 and TAB1 is inhibited in the sample compared to a control,

wherein the TAK1 is selected from the group consisting of

(i) a protein comprising amino acids 76 to 303 of SEQ ID NO:2;

(ii) a protein that binds to the TAB1 and comprises amino acids 76-303 of SEQ ID NO:2, with one to twenty amino acids substituted, deleted, and/or added; and

(iii) a protein that binds to the TAB1 and comprises an amino acid sequence encoded by a DNA sequence that hybridizes with the complement of nucleotides 408 to 1091 of SEQ ID NO:1 under washing conditions of 42°C, 5 x SSC, 0.1% sodium dodecyl sulfate, and 50% formamide; and

wherein the TAB1 is selected from the group consisting of

(iv) a protein comprising amino acids 437 to 504 of SEQ ID NO:4;

(v) a protein that binds to the TAK1 and comprises amino acids 437-504 of SEQ ID NO:4, with one to twenty amino acids substituted, deleted, and/or added; and

(vi) a protein that binds to the TAK1 and comprises an amino acid sequence encoded by a DNA that hybridizes with the complement of nucleotides 1338 to 1541 of SEQ ID NO:3 under washing conditions of 42°C, 5 x SSC, 0.1% sodium dodecyl sulfate, and 50% formamide.

62. (New) The method of claim 61, wherein the inflammatory cytokine is TNF, IL-6, or IL-10.

63. (New) A screening method comprising

(a) providing a sample comprising a TAK1 and a TAB1;

(b) contacting the sample with a compound;

(c) detecting binding between the TAK1 and the TAB1;

(d) selecting the compound if binding between the TAK1 and TAB1 is inhibited in the sample compared to a control; and

(e) testing whether the selected compound inhibits

(i) inflammation in an animal, or

(ii) inflammatory cytokine expression in an animal,

wherein the TAK1 is selected from the group consisting of

(1) a protein comprising amino acids 76 to 303 of SEQ ID NO:2;

(2) a protein that binds to the TAB1 and comprises amino acids 76-303 of SEQ ID NO:2, with one to twenty amino acids substituted, deleted, and/or added; and

(3) a protein that binds to the TAB1 and comprises an amino acid sequence encoded by a DNA sequence that hybridizes with the complement of nucleotides 408 to 1091 of SEQ ID NO:1 under washing conditions of 42°C, 5 x SSC, 0.1% sodium dodecyl sulfate, and 50% formamide; and

wherein the TAB1 is selected from the group consisting of

(4) a protein comprising amino acids 437 to 504 of SEQ ID NO:4;

(5) a protein that binds to the TAK1 and comprises amino acids 437-504 of SEQ ID NO:4, with one to twenty amino acids substituted, deleted, and/or added; and

(6) a protein that binds to the TAK1 and comprises an amino acid sequence encoded by a DNA that hybridizes with the complement of nucleotides 1338 to 1541 of SEQ ID NO:3 under washing conditions of 42°C, 5 x SSC, 0.1% sodium dodecyl sulfate, and 50% formamide.

64. (New) The method of claim 63, wherein step (e) comprises administering to the animal a lipopolysaccharide or an inflammatory cytokine.

65. (New) The method of claim 63, wherein the inflammatory cytokine is IL-1, TNF, IL-6, or IL-10.

66. (New) The method of claim 64, wherein the inflammatory cytokine administered to the animal is IL-1 or TNF.

67. (New) A screening method comprising:

(a) providing a sample comprising a TAK1 and a TAB1;

(b) contacting the sample with a compound;

(c) detecting binding between the TAK1 and the TAB1;

(d) selecting the compound if binding between the TAK1 and TAB1 is inhibited in the sample compared to a control; and

(e) identifying the selected compound as an inhibitor of inflammatory cytokine activity,

wherein the TAK1 of (a) is selected from the group consisting of

(i) a protein comprising amino acids 76 to 303 of SEQ ID NO:2;

(ii) a protein that binds to the TAB1 of (a) and comprises amino acids 76-303 of SEQ ID NO:2, with one to twenty amino acids substituted, deleted, and/or added; and

(iii) a protein that binds to the TAB1 of (a) and comprises an amino acid sequence encoded by a DNA sequence that hybridizes with the complement of nucleotides 408 to 1091 of SEQ ID NO:1 under washing conditions of 42°C, 5 x SSC, 0.1% sodium dodecyl sulfate, and 50% formamide; and

wherein the TAB1 of (a) is selected from the group consisting of

(iv) a protein comprising amino acids 437 to 504 of SEQ ID NO:4;

(v) a protein that binds to the TAK1 of (a) and comprises amino acids 437-504 of SEQ ID NO:4, with one to twenty amino acids substituted, deleted, and/or added; and

(vi) a protein that binds to the TAK1 of (a) and comprises an amino acid sequence encoded by a DNA that hybridizes with the complement of nucleotides 1338 to 1541 of SEQ ID NO:3 under washing conditions of 42°C, 5 x SSC, 0.1% sodium dodecyl sulfate, and 50% formamide.

In the abstract:

Please amend the abstract as follows:

~~Revealed are that the actions of inflammatory cytokine and the production of inflammatory cytokines such as IL-1 and TNF induced by an inflammatory stimulus as well as the production of other inflammatory cytokines such as IL-6 induced by the former class of inflammatory cytokines are all suppressed by inhibiting the signal transduction through TAK1.~~

The present invention relates to methods of screening for compounds that inhibit signal transduction by inflammatory cytokines. The methods include providing a sample that contains a TAK1 and a TAB1; contacting the sample with a compound; detecting binding between the TAK1 and the TAB1; and selecting the compound if binding between the TAK1 and TAB1 is inhibited in the sample compared to a control.